IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH,	)	
	)	
Plaintiff,	)	
	)	C. A. No. 06-222 (JJF)
v.	)	
	)	**REDACTED -**
IMPAX LABORATORIES, INC.,	)	**PUBLIC VERSION**
	)	
Defendant.	)	

VOLUME III OF IV (EXHIBITS 7-29) TO THE CONSOLIDATED DECLARATION OF KAREN JACOBS LOUDEN IN SUPPORT OF WYETH'S COUNTERSTATEMENTS IN OPPOSITION TO IMPAX'S MOTIONS FOR SUMMARY JUDGMENT

MORRIS, NICHOLS, ARSHT & TUNNELL LLP
Jack B. Blumenfeld (#1014)
Karen Jacobs Louden (#2881)
1201 N. Market Street
P.O. Box 1347
Wilmington, DE 19899-1347
(302) 658-9200
Attorneys for Plaintiff Wyeth

OF COUNSEL:

Basil J. Lewris
Linda A. Wadler
Barbara R. Rudolph
Alan A. Wright
FINNEGAN, HENDERSON, FARABOW,
GARRETT & DUNNER, L.L.P.
901 New York Avenue, N.W.
Washington, D.C. 20001
(202) 408-4000

Original Filing Date: December 28, 2007

Redacted Filing Date: January 8, 2008

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

WYETH, Plaintiff, v. IMPAX LABORATORIES, INC., Defendant.	)	C. A. No. 06-222 (JJF) **REDACTED – PUBLIC VERSION**

CONSOLIDATED DECLARATION OF KAREN JACOBS LOUDEN IN SUPPORT OF WYETH'S COUNTERSTATEMENTS IN OPPOSITION TO IMPAX'S MOTIONS FOR SUMMARY JUDGMENT

I, Karen Jacobs Louden, hereby declare as follows:

1. I am a partner with the law firm of Morris, Nichols, Arsht & Tunnell, LLP. I am one of the attorneys representing Wyeth in the current litigation.

2. Attached hereto as Exhibit 1 is a true and correct copy [redacted]

3. Attached hereto as Exhibit 2 is a true and correct copy [redacted].

4. Attached hereto as Exhibit 3 is a true and correct copy [redacted]

5. Attached hereto as Exhibit 4 is a true and correct copy [redacted]

6. Attached hereto as Exhibit 5 is a true and correct copy [redacted]

7. Attached hereto as Exhibit 6 is a true and correct copy [redacted]

8. Attached hereto as Exhibit 7 is a true and correct copy [redacted]

9. Attached hereto as Exhibit 8 is a true and correct copy [redacted]

10. Attached hereto as Exhibit 9 is a true and correct copy [redacted]

11. Attached hereto as Exhibit 10 is a true and correct copy [redacted]

12. Attached hereto as Exhibit 11 is a true and correct copy [redacted]

13. Attached hereto as Exhibit 12 is a true and correct copy [redacted]

14. Attached hereto as Exhibit 13 is a true and correct copy [redacted]

15. Attached hereto as Exhibit 14 is a true and correct copy [redacted]

16. Attached hereto as Exhibit 15 is a true and correct copy [redacted]

17. Attached hereto as Exhibit 16 is a true and correct copy [redacted]

18. Attached hereto as Exhibit 17 is a true and correct copy [redacted]

19. Attached hereto as Exhibit 18 is a true and correct copy [redacted]

20. Attached hereto as Exhibit 19 is a true and correct copy [redacted]

21. Attached hereto as Exhibit 20 is a true and correct copy [redacted]

22. Attached hereto as Exhibit 21 is a true and correct copy of a document bearing Bates Numbers WYETH208-000072 to 000095.

23. Attached hereto as Exhibit 22 is a true and correct copy [redacted]

24. Attached hereto as Exhibit 23 is a true and correct copy [redacted]

25. Attached hereto as Exhibit 24 is a true and correct copy [redacted]

26. Attached hereto as Exhibit 25 is a true and correct copy [redacted]

27. Attached hereto as Exhibit 26 is a true and correct copy [redacted]

28. Attached hereto as Exhibit 27 is a true and correct copy [redacted]

29. Attached hereto as Exhibit 28 is a true and correct copy [redacted]

30. Attached hereto as Exhibit 29 is a true and correct copy [redacted]

31. Attached hereto as Exhibit 30 is a true and correct copy [redacted]

32. Attached hereto as Exhibit 31 is a true and correct copy [redacted]

33. Attached hereto as Exhibit 32 is a true and correct copy [redacted]

34. Attached hereto as Exhibit 33 is a true and correct copy [redacted]

35. Attached hereto as Exhibit 34 is a true and correct copy [redacted]

36. Attached hereto as Exhibit 35 is a true and correct copy [redacted]

37. Attached hereto as Exhibit 36 is a true and correct copy [redacted]

38. Attached hereto as Exhibit 37 is a true and correct copy [redacted]

39. Attached hereto as Exhibit 38 is a true and correct copy [redacted]

40. Attached hereto as Exhibit 39 is a true and correct copy of the Assignment Transferring Rights to U.S. Patent No. 5,506,270 from Upton, Derivan, and Rudolph to American Home Products Corporation.

41. Attached hereto as Exhibit 40 is a true and correct copy of an article entitled J. Russell, *Relatively Low Doses of Cisapride in the Treatment of Nausea in Patients Treated with Venlafaxine for Treatment-Refactory Depression*, J. Clin. Psychopharmacology, Vol. 16, No. 1, pp. 35-37 (1996).

42. Attached hereto as Exhibit 41 is a true and correct copy of [redacted]

43. Attached hereto as Exhibit 42 is a true and correct copy of the Assignment Transferring Rights for the Patents-in-Suit from S. White to American Home Products Corporation.

44. Attached hereto as Exhibit 43 is a true and correct copy [redacted]

45. Attached hereto as Exhibit 44 is a true and correct copy [redacted]

46. Attached hereto as Exhibit 45 is a true and correct copy [redacted]

47. Attached hereto as Exhibit 46 is a true and correct copy [redacted]

48. Attached hereto as Exhibit 47 is a true and correct copy [redacted]

49. Attached hereto as Exhibit 48 is a true and correct copy [redacted]

50. Attached hereto as Exhibit 49 is a true and correct copy of excerpted pages from the 19th Edition of *Remington: The Science and Practice of Pharmacy*, (1995) Vol. II, Ch. 92.

51. Attached hereto as Exhibit 50 is a true and correct copy of [redacted]

52. Attached hereto as Exhibit 51 is a true and correct copy of an article entitled Sarkar, "*Thermal Gelation Properties of Methyl and Hydroxypropyl Methylcellulose [i.e., HPMC]*", Journal of Applied Polymer Science, Vol. 24, pp. 1073-1087 (1979).

53. Attached hereto as Exhibit 52 is a true and correct copy [redacted]

54. Attached hereto as Exhibit 53 is a true and correct copy [redacted]

55. Attached hereto as Exhibit 54 is a true and correct copy [redacted]

56. Attached hereto as Exhibit 55 is a true and correct copy [redacted]

57. Attached hereto as Exhibit 56 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Microcrystalline Cellulose, edited by R. C. Rowe et al., pp. 108-111 (4th ed. 2003).

58. Attached hereto as Exhibit 57 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Sugar Spheres, edited by R.C. Rowe et al., pp.630-631 (4th ed. 2003).

59. Attached hereto as Exhibit 58 is a true and correct copy of excerpted pages from the Handbook of Pharmaceutical Excipients: Povidone, edited by R.C. Rowe et al., pp.508-513 (4th ed. 2003).

60. Attached hereto as Exhibit 59 is a true and correct copy [redacted]

61. Attached hereto as Exhibit 60 is a true and correct copy [redacted]

62. Attached hereto as Exhibit 61 is a true and correct copy of U.S. Patent No. 5,885,616, issued on March 23, 1999.

63. Attached hereto as Exhibit 62 is a true and correct copy [redacted]

64. Attached hereto as Exhibit 63 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 08/821,137.

65. Attached hereto as Exhibit 64 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 08/964,328.

66. Attached hereto as Exhibit 65 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/488,629.

67. Attached hereto as Exhibit 66 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/884,412.

68. Attached hereto as Exhibit 67 is a true and correct copy of excerpted pages from the file wrapper for Patent Application No. 09/950,965.

I declare under penalty of perjury that the foregoing is true and correct, and that this declaration was executed on this 28th day of December, 2007.

/s/ Karen Jacobs Louden (#2881)
Karen Jacobs Louden (#2881)

1347978

CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that on January 8, 2008, I electronically filed the foregoing with the Clerk of the Court using CM/ECF, which will send notification of such filing(s) to the following:

Mary B. Matterer
MORRIS JAMES LLP

I also certify that copies were caused to be served on January 8, 2008 upon the following in the manner indicated:

BY E-MAIL AND HAND

Mary B. Matterer
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19899

BY E-MAIL

Joseph C. Gratz
Daralyn J. Durie
KEKER & VAN NEST LLP
710 Sansome Street
San Francisco, CA 94111-1704

/s/ Karen Jacobs Louden

Karen Jacobs Louden (#2881)
klouden@mnat.com

Exhibit 7

REDACTED

Exhibit 8

REDACTED

Exhibit 9

REDACTED

Exhibit 10

REDACTED

Exhibit 11

REDACTED

Exhibit 12

REDACTED

Exhibit 13

REDACTED

Exhibit 14

REDACTED

Exhibit 15

REDACTED

Exhibit 16

REDACTED

Exhibit 17

REDACTED

Exhibit 18

REDACTED

Exhibit 19

REDACTED

Exhibit 20

REDACTED

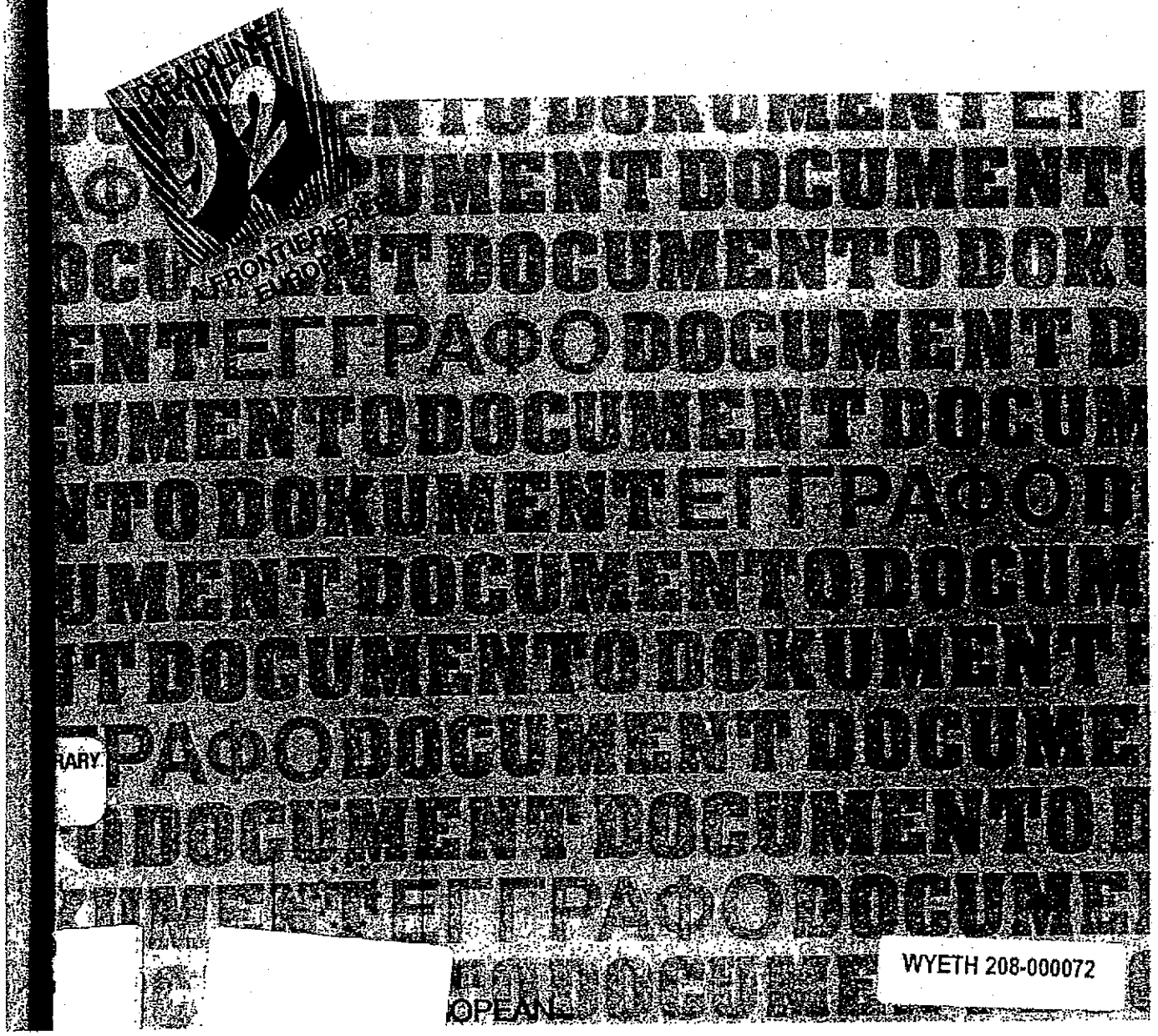
Exhibit 21

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY

Volume III

ADDENDUM JULY 1990

Guidelines on the quality, safety and efficacy of medicinal products for human use



This publication is also available in the following languages:

ES ISBN 92-826-0419-5
DE ISBN 92-826-0420-9
FR ISBN 92-826-0422-5

Cataloguing data can be found at the end of this publication.

Luxembourg: Office for Official Publications of the European Communities, 1990

ISBN 92-826-0421-7

Catalogue number: CB-59-90-936-EN-C

Printed in Belgium

Commission of the European Communities

THE RULES GOVERNING MEDICINAL PRODUCTS IN THE EUROPEAN COMMUNITY

Volume III

ADDENDUM JULY 1990

Guidelines on the quality, safety and efficacy of medicinal products for human use

Document

These Notes for Guidance, which have no legal force, have been prepared by the Committee for Proprietary Medicinal Products, in consultation with the competent authorities of the Member States, to assist applicants for a marketing authorization for a medicinal product. In case of doubt, reference should be made to the text of the relevant EEC Directives.

July 1990

COMMISSION
OF THE EUROPEAN
COMMUNITIES

GUIDELINES ON THE QUALITY, SAFETY AND EFFICACY OF MEDICINAL PRODUCTS FOR HUMAN USE

ADDENDUM

JULY 1990

FOREWORD

In 1989, the Commission published a series of five volumes entitled 'The rules governing medicinal products in the European Community'(*). Volume III of this series contains the guidelines on the quality, safety and efficacy of medicinal products for human use adopted by the Committee for Proprietary Medicinal Products up to the end of 1988. Since then, seven new guidelines have been adopted and two others revised. The Commission has therefore considered it timely to make available these new texts in the form of this addendum to volume III.

It should be recalled that these guidelines serve a two-fold objective. First, they are intended to provide a basis for a practical harmonization of the manner in which the Member States interpret and apply the detailed requirements for the demonstration of quality, safety and efficacy contained in the Community directives. Second, they are intended to facilitate the preparation of applications for marketing authorization which will be recognized as valid by all 12 Member States.

The use of guidelines, which are not legally binding, rather than a formal legal instrument, such as a directive, for this work has been preferred in order to maintain an element of flexibility and not to place undue legislative restraints on scientific progress. It is recognized that in some cases, as a result of scientific developments, an alternative approach may be appropriate. However, where an applicant chooses not to apply a guideline, that decision must be explained and justified in the Expert Reports submitted by companies in support of an application.

(*) Volume I – The rules governing medicinal products for human use in the European Community
Catalogue number CB-55-89-706-EN-C
Volume II – Notice to applicants for marketing authorizations for medicinal products for human use in the Member States of the European Community
Catalogue number CB-55-89-293-EN-C
Volume III – Guidelines on the quality, safety and efficacy of medicinal products for human use
Catalogue number CB-55-89-843-EN-C
Volume IV – Guide to Good Manufacturing Practice for the manufacture of medicinal products
Catalogue number CB-55-89-722-EN-C
Volume V – Veterinary medicinal products
Catalogue number CB-55-89-972-EN-C

TABLE OF CONTENTS

CLINICAL TESTING OF PROLONGED ACTION FORMS WITH SPECIAL REFERENCE TO EXTENDED RELEASE FORMS

1. INTRODUCTION

This note for guidance is mainly devoted to extended release forms intended to ensure a more prolonged action and should be read and interpreted in the light of Directive 75/318/EEC amended by Directive 83/570 which it is designed to supplement.

The primary purpose is to define the studies to be conducted in man, which are specific to new extended release forms containing recognized active and safe medicinal substances so as to ensure a more prolonged action than the conventional pharmaceutical forms already marketed. This note refers predominantly to solid oral forms, but may also apply to forms corresponding to other routes of administration, such as parenteral (sub-cutaneous or intramuscular) or local (transdermal, etc.) routes, intended to develop a systemic effect.

For those new forms containing well-known substances:

- it is inappropriate and unnecessary to repeat the toxicological, pharmacological or clinical tests designed to define the inherent properties of the active ingredient;

- however, it is insufficient to submit the abridged dossier applicable to medicinal products which are essentially similar to products already marketed (Directive 87/21/EEC) and presented as conventional non-modified forms.

It is necessary to investigate the properties and effects of the new delivery system. This document sets out general principles for conducting such studies in man; the precise types and number of tests to be performed have to be defined on an individual case by case basis as a function of the nature of the active ingredient, the route of administration, the type of delivery system and the pursued therapeutic indication(s).

2. BACKGROUND INFORMATION

2.1 Bases of prolonged therapeutic action:

The therapeutic effect of many active ingredients presented in conventional immediate-release pharmaceutical forms is frequently brief or relatively brief.

Although a simple increase in the unit content of the active ingredient is generally sufficient to prolong the action, it is also associated with high blood/plasma concentration peaks which are often responsible for an unacceptable level of adverse reactions. As a result, it becomes necessary to change the mode of release and to have recourse to extended release forms except in those rare cases where the active ingredient does not produce marked dose-related adverse reactions.

2.2. Definition of extended release forms:

In this document, disregarding the pharmaceutical basis of the type of dosage form, a extended release form is considered as a modified pharmaceutical form of which the release of the active ingredient and its subsequent absorption are prolonged in comparison with a conventional non modified form. It should be mentioned that the designation "extended release" is used here for the sake of simplicity to cover the above defined general mode of release for which other different terms are frequently employed on the basis of allegedly defined characteristics of the release kinetics: slow, gradual, prolonged, continuous, controlled, delayed, retard etc. forms.

The prolonged release of the active ingredient in man produces a spread of blood/plasma concentration as a function of time, with an increased apparent elimination half-life and/or reduction in peaks or achievement of a "plateau". The staggering of concentrations is accompanied by a prolongation of therapeutic action without any increase, and possibly with a reduction in adverse reactions.

2.3. Fields of application:

An extended release form can be only considered acceptable if the active ingredient simultaneously:

- is regarded as effective and safe,
- does not necessitate the repetition of high concentrations in the body and/or of daily "wash-out periods", to produce and maintain full therapeutic activity,
- has a dose-response relationship such that a high level of adverse reactions would ensue from the use of an increased active ingredient content of a conventional dose form and/or can produce the desirable clinical effect with a lower dose in an extended release preparation .

Recourse to an extended release form is generally more appropriate if the active ingredient:

- has a short, or relatively short, intrinsic elimination half-life and/or action,
- is intended for long-term treatment, the reduction in dose frequency being likely to improve compliance of patients.

2.4. Objectives of clinical testing:

Studies in man have a dual purpose, namely:

- to establish firstly that the new form definitely exhibits extended release in vivo; this is a necessary, though not always sufficient condition for obtaining a prolonged effect;

- and subsequently to verify that a prolonged therapeutic effect is achieved and that the mode of administration makes effective and safe treatment possible.

These two "validation" stages - biopharmaceutical and therapeutic - are dealt with in succession below.

3. BIOPHARMACEUTICAL VALIDATION OF THE EXTENDED RELEASE FORM

The in-vivo performances of extended release forms are generally studied after the administration of a single dose to healthy subjects on a comparative basis, taking as a reference preparation conventional forms administered by the same route (marketed conventional forms, solution or suspension prepared extemporaneously) and/or by another route of administration or a different form (e.g. intravenous perfusion and/or ointment in the case of a transdermal system). Unless otherwise justified, studies should also be performed at steady state, after repeated administration in patients or in healthy volunteers.

These bioavailability studies are mostly based on the determination of pharmacokinetic parameters, though they occasionally make use of biological or pharmacodynamic parameters (see the Note for guidance "Investigation of Bioavailability and Bioequivalence" (III/54/89)).

It is necessary to define the dosage form delivery system in terms of its rate and extent of drug delivery as well as its reproducibility.

3.1 Rate of delivery

Analysis of the profile of blood/plasma concentrations, particularly of the maximum concentrations (C_{max}) and the time of their appearance (t_{max}) and, for instance, of the duration of release estimated by the mean resident time (MRT), makes it possible to evaluate compatibility with the attainment of a prolonged effect.

3.2 Extent of delivery

Poor bioavailability may lead to an unacceptable dose-form insofar as it is likely to reduce the level of activity significantly or to increase inter-subject fluctuations unacceptably. For active ingredients with a low therapeutic index, the bioavailability of the extended release form should be close to that of the conventional form.

In the case of transdermal forms, the extent of absorption is evaluated not solely with reference both to blood/plasma or urine concentrations, but also taking into account the residual quantities of the active ingredient present in the product after the removal of the delivery system applied to the skin.

3.3 Reproducibility of in vivo performances

Variability between or within subjects significantly greater than that found using the conventional form should be taken into account in assessing the extended release forms and may constitute a possible reason for the new dose-form to be deemed unacceptable.

3.4 Special characteristics to be determined in the case of certain extended release forms

It may be necessary to study the influence of:

- diet, in the case of orally administered forms, for example to determine whether dose-dumping occurs. Where necessary, the influence of the nature of the diet and of the related changes of gastric pH should also be studied.

- the sites of application, in the case of forms applied to the skin,

If for a extended release form there are several differing dosages as regards product surface area and/or unit content, it is necessary to establish that these different presentations give identical in vivo and/or in vitro performances.

4. MEDICAL RATIONALE: THERAPEUTIC VALIDATION OF THE EXTENDED RELEASE FORM

These studies are designed to establish that forms which are satisfactory from the biopharmaceutical standpoint (see item 3) make it possible to attain the therapeutic objective in question in accordance with a particular mode of administration (dose levels and frequency):

- therapeutic activity must be maintained for the entire dosage interval between two administrations and overall for the duration of treatment; the intensity of activity is usually equivalent to or above that obtained with the conventional form; it must always be sufficient to justify the claims made with regard to indications;

- the nature, extent and frequency of adverse reactions must not cast doubt on the value of the treatment; they must be globally equivalent or inferior to those produced during treatment with the conventional form.

- any claim as to an improvement in compliance should be duly justified.

Pharmacokinetic and clinical studies should be conducted after repeated administration to patients exhibiting the stated indications. Depending on the indication(s), the influences of age, renal or hepatic impairment should be analysed.

4.1 Pharmacokinetic studies

These are conducted whenever possible and involve comparison of the extended release form with the conventional reference form at the steady state with regard (inter alia) to C_{max}, C_{min}, A.U.C., t_{max} and their fluctuations.

4.1.1 The principal objective is to verify and extend, under the recommended conditions of administration, the patient data already obtained concerning the in vivo performance of the extended release form; apparent differences in bioavailability observed after a single dose may cease to be significant at a steady state.

4.1.2 Another objective can be to establish, by inference from the blood/plasma concentrations obtained with the extended release form, that the levels of therapeutic activity and adverse reactions are equivalent to those of the reference form. Such an assumption can be made if:

a) the blood/plasma concentrations as a function of time are considered to be globally similar (equivalent) with the two forms,

and/or

b) they are situated in the therapeutic range, that is in the zone of concentrations which are generally directly associated with adequate therapeutic efficacy and the absence of marked adverse reactions.

Clinical studies may then be considered unnecessary, particularly in situation (b) where a direct relationship is recognized between plasma levels and therapeutic activity (e.g. quinidine, theophylline, ...). Nevertheless, it is useful, whenever possible, to verify the persistence of activity at the end of the dosage interval (e.g. anti-arrhythmic activity by Holter recording).

In practice, it is rarely possible to predict levels of therapeutic efficacy and/or of adverse reactions from blood/plasma concentrations, since:

- a therapeutic range is not known in the case of most active ingredients;

- the profiles of blood/plasma concentrations against time show usually an unacceptable difference for the two forms, the extended release forms producing fewer and lower peaks than conventional forms, so that the assumption a) cannot generally be made.

4.2 Therapeutic studies:

4.2.1 Objectives and principles

Therapeutic studies are necessary in the majority of cases when:

- the existence of equivalent levels of effect to those obtained with the conventional form cannot be assumed on the basis of the pharmacokinetic data (see item 4.1.);

- different therapeutic activity and/or different adverse reactions prove possible.

studies - generally comparative - should be conducted to evaluate the intensity and the duration of the therapeutic effect of a single dose and as a function of one or more dosage schedules involving multiple administration, the overall effectiveness of the treatment, adverse reactions and, possibly, the place of the new treatment among those already available on the market for the same indication. Studies should be designed and performed in order to take into account the following considerations:

a) there is a need to assess therapeutic efficacy and adverse reactions as a function of time during the complete daily cycle (24 hours) and, more particularly, at the end of dosage intervals; the possibility of development of a rapid tolerance should also be explored. The comparison should also consider what dosage regimen of the conventional forms could be replaced by the new forms.

b) the different effects of medicinal products having different dose thresholds:

- therapeutic activity is quantified with reference to the pharmacodynamic or clinical effects normally adopted as criteria for the assessment of efficacy in the concerned therapeutic class;

- an extrapolation cannot be made necessarily from one therapeutic indication to another;

c) in the case of products intended for prolonged or life-long use (see Note for Guidance on "Clinical Testing Requirements for Drugs Intended for Long-Term Use", in "The Rules Governing Medicinal Products for Human Use in the European Community", Vol. III Guidelines on the quality, safety and efficacy of medicinal products for human use, Catalogue No. CB-55-89-293-EN-C, ISBN 92-825-9619-2), courses of treatment lasting several months are necessary in order to evaluate the maintenance of efficacy, safety and compliance.

4.2.2 Studies related to efficacy and safety

Four different approaches, which are not mutually exclusive, are described below. Comparison with the standard treatment involving a validated conventional form or comparison with a placebo are the two main approaches which may be followed (see items a) and b)). However, comparison with other recognized active ingredients or with a dissimilar validated extended release form are two other possible types of study which may be performed (see items c) and d)).

a) Comparison with the standard treatment involving a validated conventional form:

Comparison between the two forms, generally on the basis of equal doses, is intended to demonstrate the equivalence or superiority of the extended release form; this approach is not without difficulties and presents the following disadvantages:

- demonstration of therapeutic equivalence will require the study to be sufficiently powerful to result in narrow confidence intervals for the difference or ratio of outcome measures using the two forms (and not just absence of a significant statistical difference).

- demonstrated equivalence relates solely to the dosage studied.

b) Comparison with a placebo:

Comparison with a placebo is particularly useful as a means of:

- demonstrating therapeutic efficacy unambiguously, given the difficulty of showing therapeutic equivalence to an active treatment,
- determining the duration of therapeutic action following a single dose and/or repeated administration,
- assessing exactly the importance of adverse reactions.

c) Comparison with other recognized active ingredients:

It may be advantageous, and even necessary, to compare the extended release form with other active ingredients which are known to be safe and effective, particularly in the case of an important innovation associated with the mode of administration, in order to assess the new product with respect to conventional treatments (e.g. glyceryl trinitrate or clonidine transdermal systems).

d) Comparison with a dissimilar validated extended release form:

The foregoing remarks on the difficulties of demonstrating the therapeutic equivalence of two forms (see a) above) also apply in this case.

4.2.3 Specific studies related to safety

Safety should be considered both in terms of systemic adverse reactions and of local irritation or sensitization and may require additional clinical testing for safety in patients.

Unless it has already been assessed during the above-mentioned studies, additional studies of <u>systemic</u> adverse reactions must be conducted under normal conditions of use; this should be especially considered when less adverse reactions are claimed for the new form.

Specific studies of <u>local</u> adverse reactions will also cover the delivery system with and without an active ingredient.

5. PARTICULAR CASES OF OTHER FORMS INTENDED TO ENSURE A PROLONGED ACTION

According to the primary goal of this Note for guidance, the previous sections were dedicated to new extended release forms containing well-known active ingredients and having a more prolonged action than the conventional forms already marketed. For the sake of completeness, this section deals briefly with other types of pharmaceutical form:

5.1. New high-dose conventional dosage form:

- These dosage forms are not prolonged action forms; nevertheless, like extended release forms, they enable less frequent administration; consequently, similar studies to those laid down for the validation of extended release forms must be conducted, comparison with the standard-dose conventional form being essential to justify the new conditions of administration.

- In view of the extent of blood/plasma peaks, special attention should be given to the investigation of adverse reactions.

5.2. Extended release form, essentially similar to a marketed, validated form:

The equivalence of the in vivo performances of the extended release forms must be demonstrated.

Acceptability studies are to be conducted where necessary; thus, the local tolerance of a transdermal system which is essentially similar to a marketed validated system must be studied, since - apart from the active ingredient - the constituent materials of the delivery system applied to the skin may be different and cause local irritation or sensitization.

5.3. New active ingredients presented from the beginning in an extended release form

The standard efficacy and safety tests applicable to all new medicinal products should be conducted in man; nevertheless, the recommendations made in this note for guidance concerning the justification and validation of the pharmaceutical form and its condition of administration also apply fully.

6. JUSTIFICATION OF THE PROLONGED-ACTION FORMS

It is useful for the dossier to indicate:

- the clinical interest of these new forms,

- and, especially in the case of these new forms, the amount of therapeutic progress achieved, linked at least with the reduction to a greater or lesser extent of the number of doses taken, simplification of treatment and possibly new indications, a reduction in adverse reactions, increase in activity and improvement in patient compliance. Proper evidence must be given for the benefits claimed.

The dossier submitted in support of an application for a marketing authorization must provide a complete justification of:

- The choice of the dosage form, defining the in vitro and/or in vivo performance of the product.

- The choice of active ingredient contents per unit of the dosage-form.

6.1 The claimed indications

For a given active ingredient, the indications for an extended release form are not automatically the same as those of the conventional forms; they may be different, thus opening up a new field of application (e.g. nitrate derivatives), or fewer in number than those of the conventional forms so that:

- the extended release form may be inadequate for the treatment of conditions requiring a rapid and short action;

- an automatic extrapolation cannot be made from one indication to another.

6.2 Conditions of administration

6.2.1 It must be made quite clear in the dossier whether or not the extended release form or its various dosages can be used:

- at the initiation of treatment at a fixed dose or with a gradual increase in the dosage, in spite of a high unit dose and/or delayed action,

- for initial treatments with one or several loading dose(s) and for acute attacks,

- for maintenance treatment(s) covering the whole range of doses normally used,

- for the treatment of special patients exposed to greater risk such as children, the elderly and persons suffering from renal or hepatic insufficiency.

Two possibilities should be considered when this balance sheet of potential uses has been compiled, namely:

a) whether the extended release form(s) can be used for all treatments in all patients covered by the indications, in which case the conventional form is no longer necessary;

b) or because the low unit content makes the conventional form(s) more "flexible" to use, they are/it is still valuable:

- when dosage has to be progressively adjusted at the beginning of treatment before the possible replacement of the conventional form by the extended release form on the basis of an equivalent dose or doses;

- in prolonged treatments where the specific doses are different from that or those studied in the dossier on the extended release form;

- in the treatment of specific types of patients: children, the elderly, those suffering from renal failure etc. and/or in the case of certain indications.

The need to have conventional forms available in conjunction with the extended release form must be made clear in the information provided, which must define as clearly as possible the situations and modes of use of the two forms so as to avoid new prescribing problems for the physician and the risk of overdosing (or underdosing) for a significant proportion of those treated.

6.2.2 Marketing authorizations cannot be granted to an applicant for an extended release form having a single unit dosage if other dosages are necessary to guarantee the therapeutic effect in the context of dose adjustment and to preclude harmful effects under normal conditions of use (e.g. theophylline).

6.2.3 The information provided must include specific recommendations aimed at ensuring optimum conditions of use (e.g. instructions not to chew or crush tablets etc.).

6.3 It is useful for the dossier to indicate:

- the clinical interest of these new forms;

- and, especially in the case of extended release forms, the amount of therapeutic progress achieved, linked at least with the reduction to a greater or lesser extent of the number of doses taken, simplification of treatment and possibly new indications, a reduction in adverse reactions, increase in activity and improvement in patient compliance and disease control. Proper evidence must be given for the benefits claimed.

Exhibit 22

REDACTED

Exhibit 23

REDACTED

Exhibit 24

REDACTED

Exhibit 25

REDACTED

Exhibit 26

REDACTED

Exhibit 27

REDACTED

Exhibit 28

REDACTED

Exhibit 29

REDACTED